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Review

Pruritus in Chronic Kidney Disease: An Update

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Abstract: Chronic kidney disease-associated pruritus (CKDaP) is an often under-diagnosed and under-recognized condition, despite its considerable prevalence within the chronic kidney disease (CKD) population. Universally accepted guidelines are also lacking. The true prevalence of CKDaP worldwide therefore remains unknown, although its negative impact on mortality and health-related quality of life outcomes is very clear. The pathophysiological mechanisms leading to the onset of CKDaP are only partly understood. CKDaP is currently believed to be caused by a multifactorial process, from local skin changes, metabolic alterations, the development of neuropathy and dysregulation of opioid pathways, and psychological factors. Much work has been carried out towards a more systematic and structured approach to clinical diagnosis. Various tools are now available to assess the severity of CKDaP. Many of these tools require greater validation before they can be incorporated into the guidelines and into routine clinical practice. Further efforts are also needed in order to increase the awareness of clinicians and patients so that they can identify the CKDaP signs and symptoms in a timely manner. Currently established treatment options for CKDaP focus on the prevention of xerosis via topical emollients, the optimization of dialysis management, early referral to kidney transplantation if appropriate, oral antihistamine, and a variety of neuropathic agents. Other novel treatment options include the following: topical analgesics, topical tacrolimus, cannabinoid-containing compounds, antidepressants, oral leukotrienes, opioids, and non-pharmacological alternative therapies (i.e., phototherapy, dietary supplements, acupuncture/acupressure). We provide an updated review on the evidence relating to the epidemiology, the pathophysiology, the clinical assessment and diagnosis, and the management of CKDaP.

Keywords: chronic kidney disease-associated pruritus; epidemiology; pathophysiology; clinical assessment and diagnosis; management

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1. Introduction

The kidney disease improving global outcomes (KDIGO) initiative classifies an individual as having CKD if the abnormalities of kidney structure or function persist for over three months, although the definition is somewhat problematic in the elderly, in which some of the decline of kidney function may be considered to be a normal part of the aging process [1]. The global burden of CKD has increased in recent years due to an aging global population and the rise of type 2 diabetes with diabetic nephropathy; moreover, the improved methods for early identification of CKD may also contribute to this [2–6]. With more than 10% of the adult population being affected by CKD at present, it is projected to become the fifth leading cause of mortality worldwide by 2040 [5]. The prevalence of patients with CKD progressing to kidney failure requiring kidney replacement therapy has increased, with registry data documenting a greater number of patients receiving dialysis

worldwide; although universal access to dialysis is lacking in many developing countries. CKD therefore constitutes as an important global health issue [7,8].

The advanced stages of CKD involve a spectrum of secondary complications, such as anemia, secondary hyperparathyroidism/CKD-mineral bone disease (CKD-MBD), malnutrition, and electrolyte disturbances [5,9]. Together with a variety of symptoms that are seen in advanced CKD, they make up the clinical syndrome of uremia, which is typically seen in patients who are close to being initiated on dialysis. Pruritus is a common and often particularly bothersome symptom in uremia, with a considerable impact on patients' symptom burden overall. The nomenclature has changed recently from "uremic pruritus" to CKD-associated pruritus (CKDaP) in order to account for the non-linear relationship between itch and the degree of uremia overall [10]. CKDaP is associated with worsened overall patient outcomes and previous studies describe not only reduced health-related quality of life (HRQoL), but also increased sleep disturbance, poorer adherence to medication and dialysis and, importantly, increased rates of depression [10,11]. Patients with CKDaP are more likely to sustain skin infections and hospitalization and their mortality is high when compared to those without CKDaP [10,11].

The pathophysiology of CKDaP remains poorly understood, despite the fact that it is such a common and important feature of advanced kidney disease. CKDaP is perceived as a multifactorial process, which is attributed to a combination of local skin and systemic factors that are observed with advanced CKD. Progress has been made in terms of a more objective and structured assessment of CKDaP [12–15]. Establishing a consensus definition of CKDaP and creating patient-reported outcome- (PRO) oriented symptom severity scales are key features of this process [16,17]. Recent research has also focused on patient-specific goals of CKDaP treatment [18]. Importantly, new options for treatment have become available very recently, particularly for the severe end of the disease spectrum [19].

In this review, we provide an update regarding the epidemiology and pathophysiology of CKDaP. We also discuss current approaches to the assessment and the diagnosis and review the common and important differential diagnoses. Finally, we evaluate the various management strategies for CKDaP and highlight the gaps in our knowledge, as well as the avenues for future research. The study selection for this narrative review encompassed the input of the following search terms: "Pruritus", "Chronic Kidney Disease-associated Pruritus", "Epidemiology", "Pathophysiology", "Clinical Assessment", "Differential Diagnoses", "Treatment", "Management", and others into search engines, including PubMed, Web of Science, EMBASE, Google Scholar, and Medline-ProQuest. The search and selection process for the references that are included in this article were independently performed by four authors (C.C.Y.W., H.H.L.W., I.P., and A.W.).

2. Epidemiology of CKDaP

The reported prevalence of CKDaP from major national and international registries is hugely variable [20–24]. This may be explained by different levels of renal and dialysis care provision, different perceptions of patients and relatives, and variable levels of awareness of CKDaP [25]. It is likely that the current studies underestimate the true prevalence of CKDaP [20–23]. For example, the dialysis outcomes and practice patterns study (DOPPS) highlighted that 17% of patients who were receiving hemodialysis (HD) did not report this to their attending clinician [21]. Only 1% of clinicians correctly estimated the prevalence range of severe pruritus in dialysis centers where the true prevalence was between 21% and 50% [21].

The epidemiological data on CKDaP within specific treatment groups for patients receiving HD, peritoneal dialysis (PD), kidney transplantation, and non-dialysis treatment are discussed herein. Across the study phases in the DOPPS, the proportion of patients with moderate to severe pruritic symptoms did not significantly differ between the study phases, hovering above 40% [20–22]. The reported prevalence of CKDaP in populations that were receiving PD is much more variable, ranging between 10% and 70% [26]. PD is highlighted as an independent risk factor for CKDaP, following adjustments for confounding variables,

such as age, body mass index, and dialysis modality [27]. Nevertheless, there were no adjustments for biochemical parameters, with this being a potentially confounding factor influencing the findings [28]. Evidence is relatively scarce on the prevalence of pruritic symptoms in post-transplant patients, though this is believed to lie between the range of 12% and 32%, according to a previous literature review of eight studies [10]. The data from the chronic kidney disease outcomes and practice patterns study (CKDOPPS) and the chronic kidney disease-renal epidemiology and information network (CKD-REIN) studies explored the prevalence of CKDaP amongst non-dialysis CKD patients [23]. The proportion of patients with moderate to extreme levels of pruritus was 24% in CKDOPPS and CKD-REIN, with up to 13% of patients experiencing severe to extreme pruritic symptoms [23]. The patients living with kidney failure have reported a 19% greater prevalence of moderate to extreme itch compared with those with stage 3 CKD [23].

There has been an emergence of epidemiological data describing the non-modifiable and modifiable risk factors of CKDaP. The earlier phases of the DOPPS data have reported higher calcium–phosphate product concentration correlating with pruritic severity amongst HD patients, though the relationship that exists between calcium–phosphate levels and pruritic symptoms remains debatable without further convincing data [21]. The evidence in regard to the impact of age, sex, ethnicity, and country of residence on CKDaP remains controversial and, therefore, further study is needed [14,20–24,28]. Multiple co-morbidities have demonstrated strong associations with increased severity of CKDaP. These included cardiovascular, lung, neurological, and chronic infectious diseases [20,28]. The relationship between diabetes mellitus and CKDaP has previously been relatively unclear, where higher and lower prevalence of CKDaP has been associated with diabetic patients, though recent studies have found that the primary cause of most cases of pruritus is prolonged poor diabetes control with altered glucose and insulin levels, subsequently causing skin dryness and neuropathy [29–31]. Large population studies also did not indicate clear associations between laboratory parameters and CKDaP prevalence [29,30]. The data remain conflicting as to how anemia parameters, serum albumin, and inflammatory markers, such as C-reactive protein, white blood cells, and cytokines, correlate with pruritus severity in CKD [20,21,28,32–35].

The negative impact of CKDaP on clinical outcomes has been concluded from major registry data. The evidence has remained consistent on the negative impact of CKDaP for HRQOL outcomes. In the DOPPS, patients receiving HD who were experiencing pruritic symptoms were more likely to report feeling washed out, having poor sleep, and depressive symptoms compared to patients without pruritic symptoms [22]. The DOPPS also generated data concluding convincing associations between CKDaP and increased all-cause, infection-, skin-, infection-, and cardiovascular-related hospitalizations and mortality [22]. The German epidemiological hemodialysis itch study (GEHIS) is another national registry study that explored the outcomes in patients with CKDaP. It highlighted the increased mortality amongst patients with CKDaP, particularly those who had skin lesions, elevated serum C-reactive protein, weaker physical conditioning, and depressive symptoms [36]. Another conclusion of interest from the GEHIS is that patients who were receiving HD with pruritic symptoms were more likely to report pain and anxiety compared to those without pruritus [24,37]. The GEHIS also noted that more than 50% of patients who were receiving HD with pruritic symptoms complained to their clinicians regarding poor sleep, though there is no statistical correlation between the grade of pruritus severity and sleep quality [24].

Given the holistic effects of CKDaP upon an individual's physical, psychological, and functional well-being, healthcare professionals should invest greater attention on the psychosocial implications of CKDaP for both patients and their caregivers [38]. In the DOPPS, CKDaP was found to be significantly associated with lower rates of employment [22]. In countries where there may not be government initiatives to provide financial support/reimbursements for patients living with chronic diseases, such as CKD, financial difficulties with unemployment may add another source of burden for patients and

their caregivers, contributing to increased depression and poorer adherence to care [39,40]. Whilst there is a relative lack of epidemiological data specifically evaluating the psychosocial implications of CKDaP at present, social deprivation has been established as an independent risk factor of negative overall outcomes in CKD [41]. We anticipate more research assessing the psychosocial implications of CKDaP going forward.

3. Pathophysiology of CKDaP

Despite acknowledging the existence of CKDaP for many years, there remains no consensus regarding the etiology and pathophysiology of this phenomenon. In general terms, chronic pruritus is defined in cases where itching symptoms persist for over six weeks and is generally classified into the following five different categories: dermatological, systemic, neurological, somatoform, and mixed origin [12–14,16,42]. CKDaP is thought to be a systemic condition that does not derive from a dermatological cause, as it occurs as the result of complex metabolic dysfunction. There are multiple pathophysiological mechanisms that are regarded to be major factors contributing towards the manifestation of CKDaP, and these mechanisms typically have overlapping characteristics (Figure 1). Such mechanisms could be categorized into the following factors: local skin changes, metabolic alterations, development of neuropathy and dysregulation of opioid pathways, and psychological factors [12–14,16].

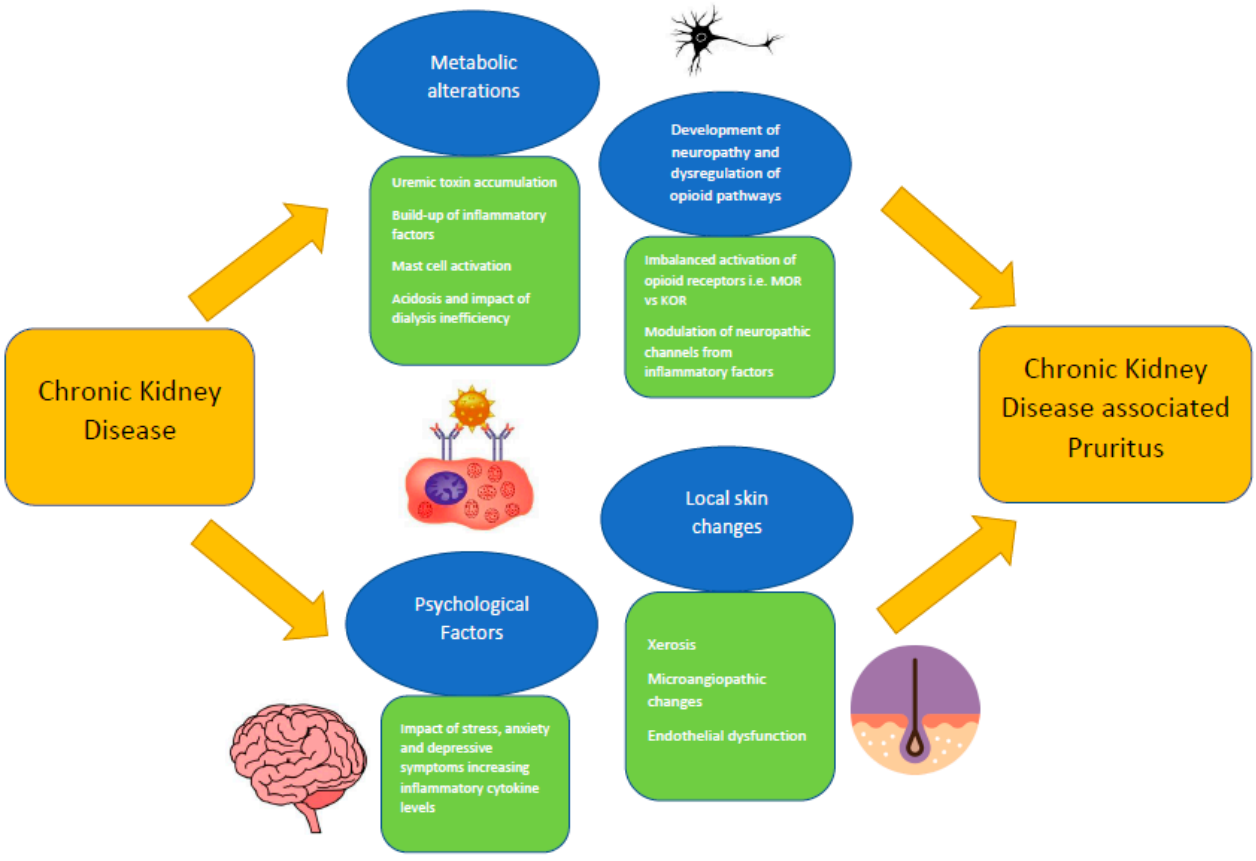


Figure 1. Overview of the pathophysiological processes of CKDaP.

Mucocutaneous changes are commonly observed in patients with CKD, and xerosis is frequently detected [43,44]. Xerosis of the skin in CKD is characterized by the atrophy of the secretory glands and a thickened basement membrane zone, resulting in an elevated pH alongside reduced hydration of the stratum corneum [45,46]. In most cases, the skin barrier function remains intact with CKD-related xerosis [47,48]. Pruritus is likely to improve with rehydration and continuous moisturization, which indicates the validity of this pathophysiological relationship [39]. Previous studies assessing skin biopsy histological

changes in CKD have noted microangiopathic changes and endothelial dysfunction [49–51]. Microangiopathy is described as a spectrum of structural remodeling of the small vessels that leads to hypoxia, increased oxidative stress, increased apoptotic activity, a reduction in viable endothelial progenitor cells, and disturbed angiogenesis [52]. Microangiopathic changes and endothelial dysfunction can cause capillary rarefication and fibrosis of the skin [52].

Uremic toxin accumulation is highlighted in numerous studies to be a major cause of CKDaP, as this affects the homeostasis of various biochemical parameters ranging from calcium, phosphate, calcitriol, parathyroid hormone (PTH), magnesium, iron, bile acids, zinc, nitric oxide, and vitamin A [20,30,53–55]. Hyperphosphatemia, hypocalcemia, and decreased calcitriol in CKD causes secondary hyperparathyroidism and, subsequently, CKD-MBD [20,30,53–55]. The findings from previous studies suggest that CKD-MBD may impact upon the onset and severity of pruritic symptoms [56]. This could be explained by the increase in calcium–phosphate product in CKD-MBD, leading to greater dermal calcium deposition, which in turn would be favored by elevated PTH levels [57]. Observations that parathyroidectomy may cure CKDaP are supportive of this pathophysiological association [58]. In addition to the uremic toxin build-up, a state of systemic micro-inflammation secondary to CKD is also thought to significantly contribute towards pruritic symptoms. Inflammatory markers, such as C-reactive protein and ferritin, and cytokines, such as interleukins: (IL-) 6, 31, and T-helper 1 cells, are documented to be elevated amongst HD patients and are recognized as factors contributing to the inflammatory process leading to CKDaP [35,59–62]. Mast cells, which generate and release histamine, tryptase, eosinophils, protease, and IL-2, have been found to be at an increased level in patients with CKDaP [12,15,30,63]. These pruritogens are instrumental in the processes of skin proliferation and degranulation, triggering an itch response [12,15]. Other factors, such as the severity of acidosis and the effects of dialysis membrane permeability in dialysis-dependent patients, have been hypothesized, but will require further validation [64–67].

For patients with kidney failure who are receiving dialysis, there is an increased prevalence of peripheral sensorimotor neuropathy and dysautonomia [68,69]. This has been investigated as a potential explanation for the occurrence of CKDaP. It was observed that pruritus can be triggered by opioid agonists that are found on the brain, peripheral nerves, keratinocytes, melanocytes, hair follicles, and immune cells (granulocytes, monocytes/macrophages, and lymphocytes) [12–14,16,70]. The three major opioid receptor types, with their corresponding ligands, are μ-opioid receptor (MOR) with endorphins, κ-opioid receptor (KOR) with dynorphins, and δ-opioid receptor (DOR) with enkephalins [71]. The KOR system is understood as an itch suppressor and the MOR system as an itch stimulator [71]. The imbalanced activation between the MOR and KOR systems is hypothesized as a mechanism of CKDaP [71]. Other receptors, such as morphine, endothelin-1, chloroquine, IL-13, and IL-31, have been proposed as key mediators of CKDaP [72,73]. The extent to which the inflammatory factors are involved in the modulation of the opioid system is also considered, given that the opioid receptors and the nerve terminals on the sensory nerves are upregulated during inflammation [74–79]. It has been suggested that the activation of the KOR system induces an anti-inflammatory response through the downregulation of cytokine, chemokine, and chemokine receptor expression [80,81]. These mechanisms are not well understood so far, therefore, there is a need for further experimental study.

The pathophysiological impact of psychological symptoms—notably stress, anxiety, and depression—have been considered to contribute towards CKDaP [82]. Associations between inflammation, depression, and itching in dialysis patients have been described, with elevated inflammatory cytokine levels (C-reactive protein, IL-1, IL-6, IL-10, and tumor necrosis factor-α) co-existing in patients with depressive symptoms [83,84].

4. Clinical Assessment and Diagnosis of CKDaP

CKDaP is formally described as a multi-systemic condition that is characterized by pruritus that is related to CKD, in addition to a diagnosis of exclusion [70]. It is crucial to

exclude all other potential alternative diagnoses before labelling one's pruritic symptoms as being down to CKDaP (Table 1). The variability in severity of its clinical presentation during the onset of disease, the time course, the distribution, the exacerbating/relieving factors, and its tendency to occur with co-existing skin manifestations makes the process of diagnosing CKDaP challenging for clinicians [42,70].

Table 1. Differential diagnoses of CKDaP.

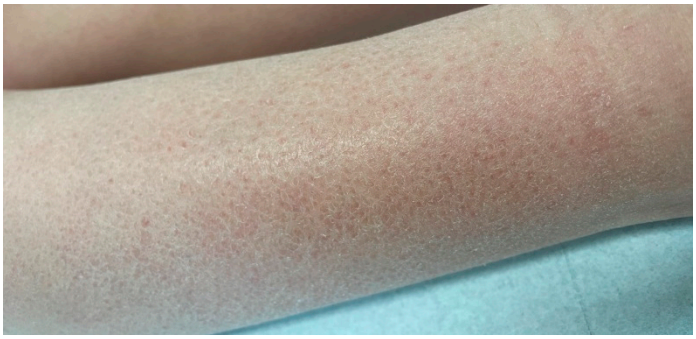
	Systemic differential diagnoses
	Autoimmune
	Dermatitis herpetiformis secondary to celiac disease
	Dermatomyositis
	Linear IgA disease
	Sjögren's syndrome
	Hematological
	Hemochromatosis
	Iron deficiency anemia
	Mastocytosis
	Plasma cell dyscrasia
	Polycythemia vera
	Hepatobiliary
	Biliary cirrhosis and sclerosing cholangitis
	Chronic pancreatitis with biliary tract obstruction
	Drug-induced cholestasis
	Hepatitis
	Systemic infections
	AIDS
	Parasites (e.g., giardiasis, onchocerciasis, schistosomiasis)
Local skin differential diagnoses	Prion disease
Allergic/irritant/contact dermatitis	**Malignancy**
Atopic dermatitis	Leukemia
Bullous pemphigoid	Lymphoma
Dermatitis herpetiformis	Multiple myeloma
Cutaneous T-cell lymphoma (mycosis fungoides)	Solid tumors with paraneoplastic syndrome
Dermatophyte infection	**Metabolic and Endocrine**
Folliculitis	Carcinoid syndrome
Lichen planus	Diabetes mellitus
Lichen simplex chronicus	Thyroid disease–hyperthyroidism and hypothyroidism
Pediculosis (lice infestation)	Hyperparathyroidism
Psoriasis	**Neurological**
Scabies	Cerebral abscess
Sunburn	Cerebral tumor
Urticaria (hives)	Multiple sclerosis
Xerosis	Stroke
	Other systemic differentials
	Drug ingestion
	Eating disorders with rapid weight loss
	Neuropsychiatric disorders
	Pregnancy

AIDS: Acquired immunodeficiency syndrome; CKDaP: Chronic kidney disease-associated pruritus; IgA: Immunoglobulin A.

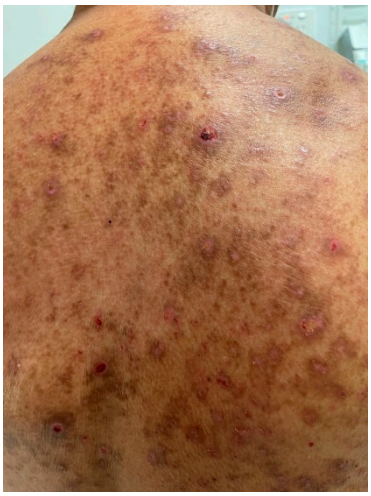
A structured, step-by-step approach beginning from thorough clinical history taking is recommended for all patients living with CKD or kidney failure in order to reduce the chances of missing a diagnosis of CKDaP [17]. This lays the foundation for further investigations to be carried out in order to guide the likely diagnosis and to rule out other potential differentials, such as cutaneous manifestations found in endocrine, infectious, rheumatological, hematological, lymphoproliferative, and neoplastic conditions [42]. For pregnant patients, pruritus may occur with greater frequency from pruritus gravidarum, or in less common scenarios due to pregnancy-related liver and cholestatic diseases [85,86].

Medication-induced pruritus is common and is also commonly overlooked in clinical practice. Opioids, angiotensin-converting enzyme inhibitors, amiodarone, estrogen-based medications, statins, hydroxyethyl starch, amiodarone, and allopurinol are amongst medications in which medication-induced pruritus has been reported [17,42].

In most instances, the skin does not display any primary lesions on clinical examination and is often found to be unchanged, unlike chronic dermatological pruritus. Most of the dermatological changes that are observed are the result of intense scratching activity by patients with CKDaP [87]. The potential lesions that are observed in CKDaP are excoriations with and without impetigo, linear crusts, papules, ulcerations, and, less commonly, prurigo nodularis (Figure 2a–c). Up to 50% of patients who were formally diagnosed with CKDaP report generalized pruritus, and the remaining percentage describe bilateral, symmetrical distribution of pruritic symptoms usually, or pruritus, which are localized to the back, face, and arms [21]. Around 25% of dialysis-dependent patients with CKDaP note the intensity of pruritic symptoms to be associated with the timing of dialysis [21]. Many of these patients found the itching to be most severe during or immediately after a dialysis session. The observational data noted that once CKDaP develops, the symptoms usually persist for months or even years [32].



(**a**)



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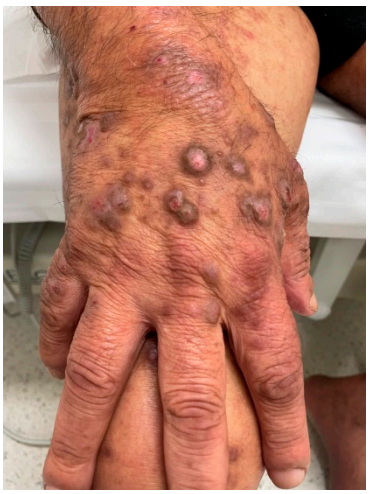

(**c**)

Figure 2. Potential skin lesions in CKDaP. (**a**) Xerosis. (**b**,**c**) Widespread prurigo nodularis, excoriations, ulcerations, and post-inflammatory hyperpigmentation.

Significant laboratory parameters that are important to observe include full the blood count, the erythrocyte sedimentation rate, the liver function, the thyroid function, the ferritin, the C-reactive protein, the infective serology, the serum cholinesterase, and the bile salts. Derangements in these metabolic parameters may indicate other potential causes of pruritus in the patient with CKD or kidney failure. For dialysis-dependent patients, it

would be helpful to monitor the dialysis efficiency (for urea clearance) and the calcium–phosphate product (for calciphylaxis and dermal calcium deposition).

An objective method to determine the intensity of skin pruritic symptoms is elusive to date and remains heavily dependent on PROs. PROs, which is defined by any report of the status of a patient's health condition that comes directly from the patient without interpretation of the patient's response by a clinician or anyone else, remains to be the recommended approach to assess the severity of CKDaP [88]. A range of unidimensional and multidimensional assessment scales have been developed in order to aid the severity classification of CKDaP when gathering PRO data, which are as follows: the visual analogue scale (VAS), the numeric rating scale (NRS), the verbal rating scale (VRS), the kidney disease QoL-short-form (KDQOL-SF), the 5D itch scale, and the dermatology life quality index [20,32,89–94].

Unidimensional assessment scales, such as VAS, NRS, VRS, and KDQOL-SF, are simple and quick to use, and they are best applied as screening tools. VAS and NRS were initially developed in order to assess the pain symptoms for patients with chronic pruritus, with VAS being more commonly utilized of the two to determine the severity of chronic pruritus [89,90]. VRS includes five scoring categories (no/low, level/moderate, level/severe, level/extreme, and severe level of itching) [91]. It possesses convertible cut-off values towards the numerical scores from VAS and NRS, which demonstrate good convergence, content validity, and strong test–retest reproducibility [90]. The KDQOL-SF survey version that is specific for CKD contains 43 question items on CKD-related symptoms, in addition to the generic 36-item short-form health survey. KDQOL-SF was initially designed in order to assess the HRQOL outcomes in patients who were receiving dialysis and is the assessment tool that is typically used in large studies evaluating CKDaP for the dialysis population [20,21].

Multidimensional assessment scales, such as the 5D itch scale, are useful in scenarios where the patients find it challenging to translate a subjective pruritus symptom into a numerical score [93]. The 5D itch scale has been validated for qualitative studies evaluating chronic pruritus symptoms. It has been shown to correlate strongly with the VAS score and is able to depict variations in pruritus symptoms in a study following up patients with CKDaP over a 6-week period [93]. Previous studies note use of the dermatology life quality index to assess pruritic symptoms in patients receiving HD [94]. The quality of life impairment component of this index correlated with uremic pruritus intensity, which was assessed with VAS and the 4-item itch questionnaire [94]. Furthermore, depressive symptom scoring significantly correlated with the quality of life and its severity was significantly associated with uremic pruritus intensity [94]. Other multidimensional assessment scales, such as the itch severity scale (ISS) and skindex-10, remain relatively less used in CKDaP and, therefore, require further validation within this context [17,95].

Increased awareness of CKDaP amongst clinicians and patients expands new horizons in establishing more methods to achieve early identification of CKDaP symptoms. Actigraphy techniques have been validated for use in skin conditions, such as atopic dermatitis [96,97]. There may be potential for actigraphy to be applied within the CKDaP setting in order to monitor the symptoms, utilizing recent advances in medical technology [98]. Clinicians and patients have a shared responsibility to ensure the report of pruritic symptoms that occur regularly, and international guidelines should endeavor to provide improved guidance on the assessment and diagnosis of CKDaP with emerging evidence.

5. Prevention and Treatment of CKDaP

There are numerous pharmacological and non-pharmacological treatment options for CKDaP, but high-quality evidence that could be used to recommend one treatment approach over another is lacking and guidelines are sparse or non-existent, leading to a situation where, in effect, most nephrologists and departments have their own favored approach. An objective interpretation of the data from most studies is complicated by the variable methods of the outcomes assessment that is employed, and a lack of direct

comparison between the different treatments. Another issue that has hampered research is that topical emollients, which are a mainstay of CKDaP treatment, are inexpensive and are, therefore, unattractive to the industry when it comes to funding large-scale clinical trials.

Given the burden of symptoms that are caused by CKDaP, and the fact that the symptoms can be debilitating, it is important to prioritize the prevention of CKDaP. The patients should be educated on good general skin care measures, such as avoiding soap-based cleansers, scratching (ideally keeping the fingernails short and clean), and triggers such as heat and stress. Additionally, a topical emollient should be considered for all patients with CKD, due to its ability to prevent the exacerbation of xerosis, which is highly prevalent in CKD and is a major contributor towards CKDaP [89,99]. Emollients with higher water content have been generally recommended. A previous study demonstrated a strong efficacy from the daily application of an aqueous gel containing 80% water content, with significant reductions in VAS over two weeks [100]. Another small, randomized trial assessing the outcomes over one week found a reduction in pruritic symptoms with an emollient regime containing oil/water emulsion and glycerol/paraffin compared to oil/water emulsion alone amongst patients with CKD [101]. Topical ointments containing omega 3- and omega 6-fatty acid and oiled bath preparations have demonstrated potential in the treatment of pruritic symptoms in CKD in recent studies, however, this requires more extensive validation [102–104]. The specific evidence in regard to topical corticosteroid administration for CKDaP does not appear to be convincing at present, but topical corticosteroids are known to be effective for generalized pruritus (whether presenting with skin lesions or not), hence, they are commonly prescribed by clinicians who are caring for patients complaining of pruritic symptoms [105].

Urea clearance and the effective management of CKD-associated complications are important aspects of treatment in order to reduce the severity of CKDaP symptoms. For dialysis-dependent patients, optimizing the uremic toxin removal through a trial of increased dialysis dosing should be the first step of CKDaP management [67,99]. Previous data remain controversial in regard to the optimal dialysis membrane and Kt/V targets to improve the pruritic symptoms for patients receiving HD [67,106]. Kt/V ('K' represents the dialyzer clearance of urea; 't' represents the duration of the dialysis session; 'V' represents the volume of the distribution of urea, which is approximately equal to patient's total body water) is a non-dimensional number and scaling parameter that been used as a measure of dialysis efficacy in a session of peritoneal dialysis (PD) or HD [107]. Increasing 'K' by improving the vascular access in order to achieve a better blood flow rate during dialysis and increasing 't' through extending dialysis for a longer period in each dialysis session are considered to be ways of improving the overall Kt/V [108]. However, the urea accumulation and removal are affected by a broad spectrum of factors, which can confound the accuracy of Kt/V [109]. There remains ongoing work to find solutions to improve the utilization of Kt/V in dialysis practices.

Most, if not all, of the reported studies relating to dialysis-dependent patients with CKDaP have small sample sizes, and therefore larger, prospective, multi-center studies are needed in order to determine the optimal dialysis regime for this group. Kidney transplantation, if it is appropriate for the individual patient with kidney failure, appears to be a superior treatment option to dialysis due to its potential to restore kidney function and to significantly improve uremic clearance and the CKD-associated complications [70,110]. Small prospective cohort studies have illustrated consistency in the resolution of pruritic symptoms and skin changes for previous CKDaP patients who underwent kidney transplantation [111–113]. The post-transplant skin biopsies found the previously noticeable uremic skin alterations to have been resolved [110,111]. If the non-dialysis conservative management of CKD is deemed to be the most suitable option, then there should be a primary focus on reducing the risks and the impacts of CKD-associated complications, such as CKD-MBD [99]. Whilst dietary phosphate restriction and calcium-based/aluminum-based/phosphate-binding medications are commonly prescribed first-line treatment op-

tions, parathyroidectomy may be utilized in severe cases when the patients are refractory to dietary and medical therapy [114,115].

CKDaP is labelled as being resistant if the symptoms persist despite measures to optimize dialysis and metabolic parameters are undertaken, and where at least a 4-week application of topical emollients and other topical alternatives have failed to resolve the symptoms [116]. In these situations, commencing systemic treatment is often recommended, starting with the prescription of oral antihistamines [117]. Oral antihistamine medications, such as hydroxyzine, are increasingly prescribed for patients with generalized pruritus and are believed to have beneficial effects, such as their sedating properties and their ability to stabilize mast cell membranes [118]. There remains limited data on the efficacy of oral antihistamine medications, specifically for CKDaP. The diminished anti-pruritic effects of oral antihistamines towards CKDaP, in comparison to generalized pruritus, supports the theory that the pathogenesis of CKDaP may be independent of the histamine pathway [119]. This will require further investigation.

Other systemic treatment options include the use of neuropathic agents, such as gabapentin and pregabalin. The pharmacokinetic action of these medications is based on the modulation of the alpha-2-delta subunit of voltage-gated calcium channels and/or the inhibition of calcitonin gene-related peptide release from sensory neurons and a reduction in neural sensitization [117,120–123]. Further work is needed in order to establish the clinical efficacy of these medications in reducing CKDaP.

The development of novel therapies to widen the options of CKDaP management has rapidly evolved over recent years. The use of topical analgesic agents, such as pramoxine and capsaicin, are suggested to have potential. These agents can block the conduction of nerve impulses in the skin layer [124–126]. Decreased neuropathic sensation and increased numbness may alleviate the pruritus symptoms [124–126]. Capsaicin is usually only used to treat localized pruritus and is not suitable in the context of generalized pruritus [99]. Topical tacrolimus is less frequently prescribed for CKDaP, despite being previously considered for its positive effects [99]. This is presumably due to concerns regarding its long-term adverse effects (particularly the increased risk of skin malignancies), despite its anti-inflammatory properties [127]. Research on the use of cannabinoid-containing compounds, such as cannabidiol and tetrahydrocannabinol, in the treatment of CKDaP have emerged [128]. Independent and randomized controlled trials (RCT) are needed in order to further evaluate its long-term effects on CKDaP management. Antidepressants, such as sertraline and doxepin, for older patients have been validated for the management of generalized pruritus, and data is emerging regarding their efficacy to manage CKDaP, despite the pharmacological mechanisms not being fully known within this context [129–131]. As depression is common amongst patients living with CKD and kidney failure, prescribing antidepressants may have a significant benefit. Oral leukotrienes, such as montelukast, may display benefits by acting on the inflammation-mediated pathway of CKDaP [132]. More work is expected to develop the potential of oral leukotrienes for the treatment of CKDaP.

With growing evidence supporting the role of opioid receptors in the pathogenesis of CKDaP, opioid medications that antagonize MOR, and/or agonize the KOR, may become an attractive treatment option, however, the results from clinical trials so far have been controversial in regard to its efficacy. We will limit our discussion to nalfurafine, difelikefalin, and nalbuphine. Nalfurafine, which is a peripheral KOR agonist, has demonstrated significant improvements in reducing CKDaP, according to the conclusions from RCTs evaluating management regimes in patients with CKDaP [133–135]. Nalfurafine is currently approved to treat resistant CKDaP in Japan. Difelikefalin is an analgesic opioid peptide that was approved in the United States in August 2021. The largest RCT on difelikefalin to date is the KALM-1 trial, where 378 maintenance hemodialysis patients with CKDaP were assigned to either IV difelikefalin (0.5 μg/kg) or a placebo three times a week post-dialysis for 12 weeks [20]. Difelikefalin is a peripherally restricted selective KOR agonist. At 12 weeks, 38% of the patients who received treatment reported an improvement in pruritic symptoms, with significant improvements in HRQOL compared to the placebo group. In

the KALM-1 clinical trial, the improvement of pruritic symptoms was defined as a >3 point reduction from the baseline in weekly a mean score on the 24 h worst itch numeric rating scale [20]. An increased frequency of side effects, such as dizziness, diarrhea, vomiting, and nasopharyngitis, were reported in the KALM-1 trial from individuals who were assigned to the intervention arm; however, no reports of any opioid-related side effects (i.e., dysphoria, euphoria, hallucinations with treatment, or symptoms of withdrawal upon discontinuation of the drug) were noted [20]. It is important to stress that difelikefalin is only available as an intravenous preparation and, therefore, it is likely to be used in patients on maintenance HD where it can be given during the treatment sessions. It is possible that this drug will become more commonly used in HD patients with CKDaP, especially those at the moderate to severe end of the spectrum and where other treatments have failed to control the symptoms. Another open-label, dose-escalated study looking at nalbuphine, which is a mixed MOR antagonist/KOR agonist, showed a reduction in the mean VAS from 4.0 to 1.2 with a nalbuphine dosage of 180 mg/day and 4.0 to 0.4 with a nalbuphine dosage of 240 mg/day [136]. The study reported no significant differences in the the VAS between the placebo and a nalbuphine dosage that was prescribed at 60 mg/day at the eight-week follow-up [136]. The conclusion of the positive effects in reducing the pruritic symptoms for HD patients following the use of nalbuphine in increased doses was also supported by another multi-center, randomized, double-blinded study comparing patient use of a nalbuphine dosage 120 mg and 60 mg tablets/day with a placebo [137]. Small sample-sized, uncontrolled studies have demonstrated the beneficial value of naloxone and naltrexone for CKDaP treatment; however, no significant advantages of using these opioid medications compared with the placebo were found in a randomized, double-blinded placebo-controlled crossover study [138–140].

In addition to the rapid development of pharmacological treatment options for CKDaP, there have been greater efforts to explore the potential of non-pharmacological therapy as well. Phototherapy has displayed effectiveness for CKDaP, however, this has only been reported in small or non-randomized studies [141,142]. The efficacy of phototherapy within this context is thought to be attributed to its ability to decrease pro-inflammatory cytokine levels and to induce mast cell apoptosis through the inhibition of T-helper 1 and 2 responses [143]. Nevertheless, phototherapy may lead to increased carcinogenic risks and is not a suitable option for patients who are receiving long-term immunosuppressive treatment [144]. Supplementary therapies, such as turmeric, zinc, activated charcoal, acupuncture, and acupressure, have been studied in relation to their effects on pruritus symptoms in CKD [145–149]. Though the initial evidence reported improvement in pruritic symptoms for users, many of these studies have significant flaws or biases in their methodology. Therefore, more validating data is required before these options are to be deemed valid for CKDaP management.

6. Future Directions for Patient-Centered Care in CKDaP

Recent years have seen increased emphasis on employing a more patient-centered and goal-orientated approach in managing CKD and its associated complications [18]. International nephrology initiatives, such as kidney disease improving global outcomes (KDIGO) and standardized outcomes in nephrology (SONG), have highlighted the assessment and management of CKDaP as being an important theme to focus on in future research [18,150]. A consensus algorithmic toolkit to guide CKDaP assessment and management is not available at present due to the lack of convincing data and universally accepted guidelines. There are numerous aspects of care that could be improved (Table 2). Clinicians of all grades should be encouraged to regularly screen for CKDaP symptoms during, essentially all, or at least most patient consultations. Examination of the entire skin should be more commonly performed in these settings, such as in dialysis clinics, although clinicians need to bear in mind that skin lesions may not be present despite ongoing CKDaP symptoms. Such efforts could also involve nursing and other ancillary staff; moreover, hemodialysis units could, for example, make it one of the questions that nurses ask the patient when they needle

them and connect them to the dialysis machine. Greater efforts could also be made to design patient-friendly information resources in order to improve the awareness of CKDaP for the CKD patient population and for their families. Creating simple scoring systems to diagnose and measure the severity of CKDaP symptoms that could be performed in community medical settings for both non-dialysis and dialysis-dependent patients would be helpful. This could help clinicians when deciding the appropriate next steps of management and whether further referral to dermatology may be required. Establishing locally accepted guidelines and pathways of liaison between nephrologists, general practitioners, and dermatologists would also greatly enhance communication and would improve the effectiveness of the care of patients with CKDaP.

Table 2. Future directions for patient-centered care in CKDaP.

Regular screening for symptoms associated with CKDaP during every patient consultation and performing skin examination
Designing patient-friendly resources (e.g., leaflets, e-resources) to improve awareness of CKDaP for the CKD population
Increasing awareness regarding CKDaP among families/carers
Creation of easy-to-use electronic scoring systems for diagnosis and severity measurement of CKDaP for use at the bedside or in the community
Development of accepted guidelines on the management of CKDaP (in the absence of internationally accepted guidelines these could be locally agreed)
Setting up video consultations with a dermatologist as part of care pathways for CKDaP, for example to monitor the response to treatment
Improve pathways of communication between nephrologists and dermatologists to increase the effectiveness and flow of care.
Involvement of other stakeholders, such as general practitioners, nursing staff etc., to improve awareness of CKDaP

CKD: Chronic kidney disease; CKDaP: Chronic kidney disease-associated pruritus.

7. Conclusions

CKDaP is a very common, but often under-diagnosed, feature of advanced CKD. Itching can be very troublesome in a small number of patients and can become debilitating to the point where a patient is severely affected in terms of their quality of life. Once experienced, the sight of a patient with advanced CKD covered in skin lesions and scratching themselves constantly during even a brief consultation is unlikely to be forgotten. Patients are often reluctant to volunteer these symptoms or fail to link them to their kidney condition. Some patients also experience shame and embarrassment or have just gotten used to the fact that their skin itches. CKDaP is also under-appreciated by care providers, not least because it is often missed or is considered intellectually less interesting than other topics. It is therefore not surprising that CKDaP is often absent from the teaching of younger nephrologists, medical students, and nursing staff who are based in the nephrology specialty. CKDaP is also easily overlooked, for example when patients are not examined in detail or when they are seen in virtual and remote settings of care. It is equally troubling that our understanding of the pathophysiology of CKDaP is still incomplete, although some advances have been made, mainly with respect to the role of opioid receptors, leading to new substances for the treatment of CKDaP. It is likely that some of those, such as difelikefalin, will become standard for the of care for some patients with CKDaP. Prevention is also important, and we would suggest that severe CKDaP can be prevented in the majority of patients with good general skin care measures, including the regular use of topical emollients, and by optimizing the management of CKD and its associated complications. Regularly consulting patients about itchy skin and performing clinical examination also helps clinicians to identify patients with pruritic symptoms early on. A multi-faceted approach is probably needed in order to improve the situation for patients

and targeted patient information on CKDaP for all patients with advanced CKD should be considered. The teams that are looking after patients with advanced CKD should make it their mission to have CKDaP on their radar, agree on local guidance for the diagnosis and treatment, and offer a multi-disciplinary approach for patients with severe symptoms.

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